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(54) Title: [5-CARBOXAMIDO OR 5-FLUORO]-[2',3'-UNSATURATED OR 3'-MODIFIED]-PYRIMIDINE NUCLEOSIDES

(57) Abstract

A method and composition for the treatment of HIV an HBV infections in humans and other host animals is disclosed that includes the administration of an effective amount of a [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleoside or a [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleoside, mixtures thereof, or a pharmaceutically acceptable derivative or derivatives thereof, including an N-1 or N-4 alkylated or acylated derivative, or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier.

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[5-CARBOXAMIDO OR 5-FLUORO]-[2',3'-UNSATURATED OR 3'-MODIFIED]-PYRIMIDINE NUCLEOSIDES

Background of the Invention

This invention is in the area of biologically active nucleosides, and specifically includes antiviral compositions that include a [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleoside or [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleoside, or its physiologically acceptable derivative, or physiologically acceptable salt.

In 1981, acquired immune deficiency syndrome (AIDS) was identified as a disease that severely compromises the human immune system, and that almost without exception leads to death. In 1983, the etiological cause of AIDS was determined to be the human immunodeficiency virus (HIV). The World Health organization estimates that currently 13 million people worldwide are infected with HIV and that forty million people will be infected by the year 2000. Each day approximately 5,000 people are newly infected.

In 1985, it was reported that the synthetic nucleoside 3'-azido-3'-deoxythymidine (AZT) inhibits the replication of human immunodeficiency virus. Since then, a number of other synthetic nucleosides, including 2',3'-dideoxyinosine (DDI), 2',3'-dideoxycytidine (DDC), and 2',3'-dideoxy-2',3'-didehydrothymidine (D4T), have been proven to be effective against HIV. After cellular phosphorylation to the 5'-triphosphate by cellular kinases, these synthetic nucleosides are incorporated into a growing strand of viral DNA, causing chain termination due to the absence of the 3'-hydroxyl group. They can also inhibit the viral enzyme reverse transcriptase.

The success of various synthetic nucleosides in inhibiting the replication of HIV *in vivo* or *in vitro* has led a number of researchers to design and test nucleosides that substitute a heteroatom for the carbon atom

at the 3'-position of the nucleoside. Norbeck, et al., disclosed that (±)-1-[(2ß,4ß)-2-(hydroxymethyl)-4-dioxolanyl]thymine (referred to as (±)-dioxolane-T) exhibits a modest activity against HIV (EC_{50} of 20 μM in ATH8 cells), and is not toxic to uninfected control cells at a concentration of 200 μM. Tetrahedron Letters 30 (46), 6246, (1989). European Patent Application Publication No. 0 337 713 and U.S. Patent No. 5,041,449, assigned to BioChem Pharma, Inc., disclose racemic 2-substituted-4-substituted-1,3-dioxolanes that exhibit antiviral activity.

U.S. Patent No. 5,047,407 and European Patent Application Publication No. 0 382 526, also assigned to BioChem Pharma, Inc., disclose that a number of racemic 2-substituted-5-substituted-1,3-oxathiolane nucleosides have antiviral activity, and specifically report that the racemic mixture of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (referred to below as BCH-189) has approximately the same activity against HIV as AZT, and little toxicity. BCH-189 has also been found to inhibit the replication of AZT-resistant HIV isolates in vitro from patients who have been treated with AZT for longer than 36 weeks. The (-)-enantiomer of the ß-isomer of BCH-189, known as 3TC, which is highly potent against HIV and exhibits little toxicity, has been approved for the treatment of HIV in humans by the U.S. Food and Drug Administration in combination with AZT.

It has also been disclosed that cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane ("FTC") has potent HIV activity. Schinazi, et al., "Selective Inhibition of Human Immunodeficiency viruses by Racemates and Enantiomers of cis-5-Fluoro-l-[2-(Hydroxymethyl)-1,3-Oxathiolane-5-yl]Cytosine" Antimicrobial Agents and Chemotherapy, November 1992, page 2423-2431. See also U.S. Patent No. 5,210,085; U.S. Patent No. 5,204,466, WO 91/11186, and WO 92/14743.

Another virus that causes a serious human health problem is the hepatitis B virus (referred to below as "HBV"). HBV is second only to tobacco as a cause of human cancer. The mechanism by which HBV induces

cancer is unknown. It is postulated that it may directly trigger tumor development, or indirectly trigger tumor development through chronic inflammation, cirrhosis, and cell regeneration associated with the infection.

After a two to six month incubation period in which the host is unaware of the infection, HBV infection can lead to acute hepatitis and liver damage, that causes abdominal pain, jaundice, and elevated blood levels of certain enzymes. HBV can cause fulminant hepatitis, a rapidly progressive, often fatal form of the disease in which massive sections of the liver are destroyed.

Patients typically recover from acute hepatitis. In some patients, however, high levels of viral antigen persist in the blood for an extended, or indefinite, period, causing a chronic infection. Chronic infections can lead to chronic persistent hepatitis. Patients infected with chronic persistent HBV are most common in developing countries. By mid-1991, there were approximately 225 million chronic carriers of HBV in Asia alone, and worldwide, almost 300 million carriers. Chronic persistent hepatitis can cause fatigue, cirrhosis of the liver, and hepatocellular carcinoma, a primary liver cancer.

In western industrialized countries, high risk groups for HBV infection include those in contact with HBV carriers or their blood samples. The epidemiology of HBV is very similar to that of acquired immune deficiency syndrome, which accounts for why HBV infection is common among patients with AIDS or AIDS related complex. However, HBV is more contagious than HIV.

Both FTC and 3TC exhibit activity against HBV. Furman, et al., "The Anti-Hepatitis B Virus Activities, Cytotoxicities, and Anabolic Profiles of the (-) and (+) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-oxathiolane-5-yl]-Cytosine" Antimicrobial Agents and Chemotherapy, December 1992, page 2686-2692; and Cheng, et al., Journal of Biological Chemistry, Volume 267(20), 13938-13942 (1992).

A human serum-derived vaccine has been developed to immunize patients against HBV. While it has been found effective, production of the vaccine is troublesome because the supply of human serum from chronic carriers is limited, and the purification procedure is long and expensive. Further, each batch of vaccine prepared from different serum must be tested in chimpanzees to ensure safety. Vaccines have also been produced through genetic engineering. Daily treatments with α- interferon, a genetically engineered protein, has also shown promise.

In light of the fact that acquired immune deficiency syndrome, AIDS-related complex, and hepatitis B virus have reached epidemic levels worldwide, and have tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat these diseases that have low toxicity to the host.

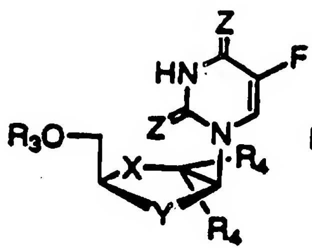
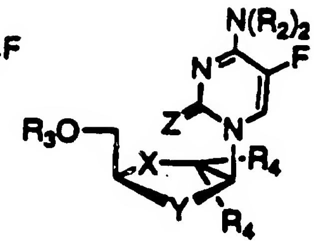
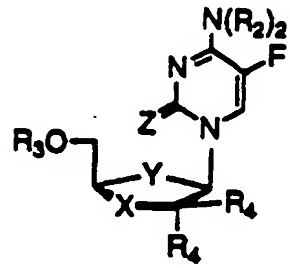
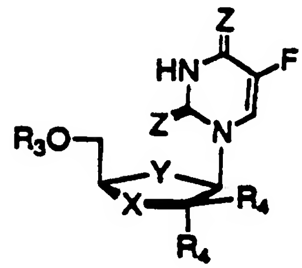
Therefore, it is an object of the present invention to provide a method and composition for the treatment of human patients infected with HIV.

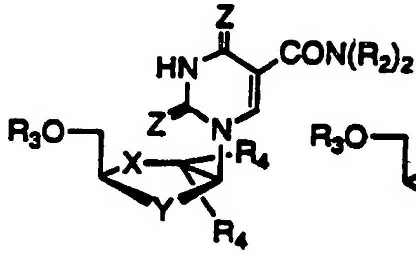
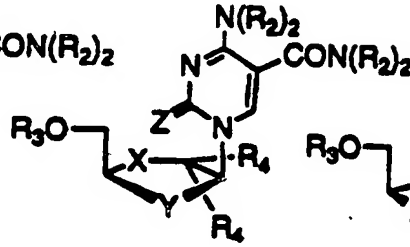
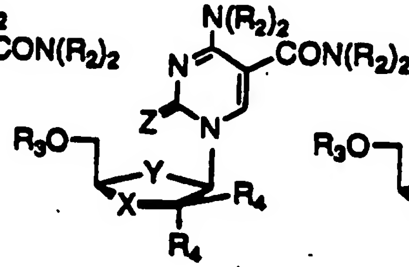
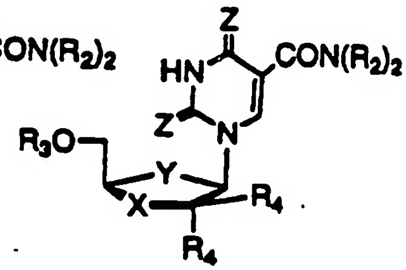
It is another object of the present invention to provide a method and composition for the treatment of human patients or other host animals infected with HBV.

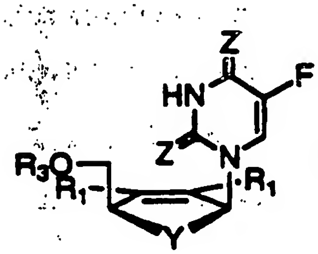
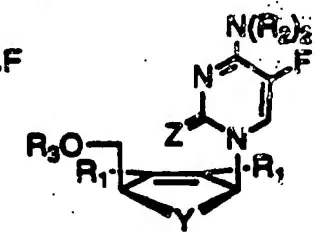
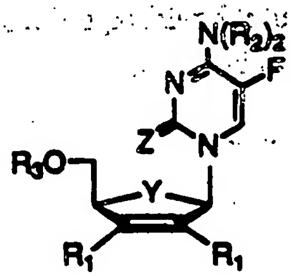
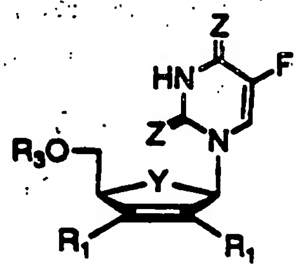
Summary of the Invention

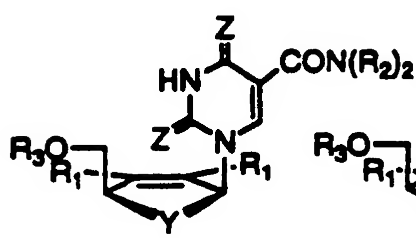
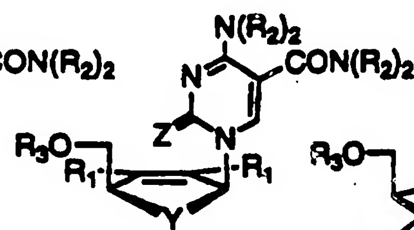
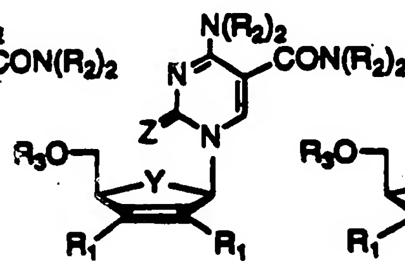
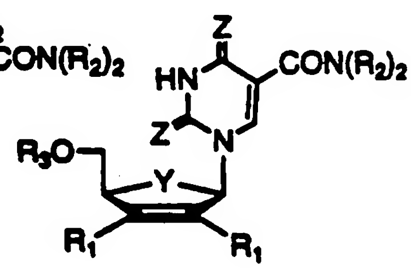
A method and composition for the treatment of HIV and HBV infections in humans and other host animals is disclosed that includes the administration of an effective amount of a [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleoside, or a [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleoside, or a mixture or a pharmaceutically acceptable derivative thereof, including a 5' or N^4 alkylated or acylated derivative, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

Specifically, compounds of the structure:

wherein: X is O, S, CH_2, CHF, or CF_2;

Y is O, S, CH_2, CHF, CF_2;

Z is independently O, S or Se;

R_1 is independently H or F;

R_2 is independently H, OH, C_1 to C_6 alkyl, or $C(O)(C_1$ to C_6 alkyl);

R_3 is H, $C(O)(C_1-C_6$ alkyl); alkyl, or mono-, di- or triphosphate; and

R_4 is independently H, F, C1, Br, I, OH, $O(C_1-C_6alkyl)$, -SH, $-S(C_1-C_6alkyl)$; or $-C_1-C_6alkyl$.

In a preferred embodiment for 2',3'-dideoxy-2',3'-didehydro-nucleosides, Y is O or S; Z is O; R_1 is H; R_2 is H; and R_3 is H. In a preferred embodiment for the 3'-modified pyrimidine nucleosides, X is O or S; Y is O; Z is O; R_1 is H; R_2 is H; R_3 is H, and R_4 is independently H or F. The term "independently" means that the groups can vary within the compound.

In the above formula, when Y is O, X is O or S; and R^4 is H, the 5-substituent is preferably not fluorine.

Preferred compounds include the racemic mixture, ß-D and ß-L isomers of the following compounds: 2-hydroxymethyl-5-(N-5'-carboxamidouracil-1'-yl)-1,3-oxathiolane; 2-hydroxymethyl-4-(N-5'-carboxamidouracil-1'-yl)-1,3-dioxolane; 2-hydroxymethyl-4-(N-5'-fluorocytosin-1'-yl)-1,3-dithiolane; 2-hydroxymethyl-4-(N-5'-carboxamidouracil-1'-yl)-1,3-dithiolane; 2-hydroxymethyl-4-(N-5'-fluorocytosin-1'-yl)-1,3-oxathiolane; 2-hydroxymethyl-4-(N-5'-carboxamidouracil-1'-yl)-1,3-oxathiolane; 2',3'-dideoxy-2',3'-didehydro-5-fluorocytidine; 2',3'-dideoxy-2',3'-didehydro-5-carboxamidocytidine; 2',3'-dideoxy-5-fluorocytidine; 2',3'-dideoxy-5-carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro-2',5-difluorocytidine; 2',3'-dideoxy-2',3'-didehydro-2'-fluoro-5-carboxamidocytidine, 2',3'-dideoxy-2',3'-didehydro-3',5-difluorocytidine; 2',3'-dideoxy-2',3'-didehydro-3'-fluoro-5-

carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro-2',3',5-trifluoro-cytidine; 2',3'-dideoxy-2',3'-didehydro-2',3'-difluoro5-carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro-5-fluorocytidine; 2',3'-dideoxy-2',3'-didehydro-5-carboxamidocytidine; 2',3'-dideoxy-5-fluorocytidine; 2',3'-dideoxy-5-carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro-2',5-difluorocytidine; 2',3'-dideoxy-2',3'-didehydro-2'-fluoro-5-carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro-3',5-difluorouridine; 2',3'-dideoxy-2',3'-didehydro-3'-fluoro-5-carboxamidouridine; 2',3'-dideoxy-2',3'-didehydro-2',3',5-trifluorouridine; and 2',3'-dideoxy-2',3'-didehydro-2',3'-difluoro-5-carboxamidouridine.

In another embodiment, the active compound or its derivative or salt can be administered in combination or alternation with another antiviral agent, such as an anti-HIV agent or anti-HBV agent, including those described above. In general, during alternation therapy, an effective dosage of each agent is administered serially, whereas in combination therapy, an effective dosage of two or more agents are administered together. The dosages will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC); the (-)-enantiomer of 2-hydroxymethyl-5(cytosin-1-yl)-1,3-oxathiolane (3TC); carbovir, acyclovir, interferon, famciclovir, penciclovir, AZT, DDI, DDC, D4T, L-(-)-FMAU, CS-92 (3'-azido-2',3'-dideoxy-5-methyl-cytidine), and β-D-dioxolane nucleosides such as β-D-dioxolanyl-guanine (DG), β-D-dioxolanyl-2,6-diaminopurine (DAPD), and β-D-dioxolanyl-6-chloropurine (ACP).

The compounds can also be used to treat equine infectious anemia virus (EIAV), feline immunodeficiency virus, and simian imunodeficiency virus. (Wang, S., Montelaro, R., Schinazi, R.F., Jagerski, B., and Mellors, J.W.: Activity of nucleoside and non-nucleoside reverse transcriptse inhibitors (NNRTI) against equine infectious anemia virus (EIAV). First National Conference on Human Retroviruses and Related Infections, Washington, DC, Dec. 12-16, 1993; Sellon D.C., Equine Infectious Anemia, Vet. Clin. North Am. Equine Pract. United States, 9: 321-336, 1993; Philpott, M.S., Ebner, J.P., Hoover, E.A., Evaluation of 9-(2-phosphonylmethoxyethyl) adenine therapy for feline immunodeficiency virus using a quantative polymerase chain reaction, Vet. Immunol. Immunopathol. 35:155166, 1992.)

Detailed Description of the Invention

As used herein, the term "enantiomerically enriched nucleoside" refers to a nucleoside composition that includes at least 95% to 98%, or more preferably, 99% to 100%, of a single enantiomer of that nucleoside.

The term C_1-C_6 alkyl includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl.

The invention as disclosed herein is a method and composition for the treatment of HIV and HBV infections, and other viruses replicating in like manner, in humans or other host animals, that includes administering an effective amount of a [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleoside or [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleoside, a pharmaceutically acceptable derivative, including a 5' or N^4 alkylated or acylated derivative, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

The compounds of this invention either possess antiviral activity, such as anti-HIV-1, anti-HIV-2, anti-HBV, and anti-simian immunodeficiency virus (anti-SIV) activity themselves or are metabolized to a compound that exhibits antiviral activity.

The disclosed compounds or their pharmaceutically acceptable derivatives or salts or pharmaceutically acceptable formulations containing these compounds are useful in the prevention and treatment of HIV infections and other related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-related neurological conditions, anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections. In addition, these compounds or formulations can be-used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HIV antibody or HIV-antigen positive or who have been exposed to HIV.

The compound or its pharmaceutically acceptable derivatives or salt, or pharmaceutically acceptable formulations containing the compound or its derivatives or salt, are also useful in the prevention and treatment of HBV infections and other related conditions such as anti-HBV antibody positive and HBV-positive conditions, chronic liver inflammation caused by HBV, cirrhosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue. These compounds or formulations can also be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HBV antibody or HBV antigen positive or who have been exposed to HBV.

The compound can be converted into a pharmaceutically acceptable ester by reaction with an appropriate esterifying agent, for example, an acid halide or anhydride. The compound or its pharmaceutically acceptable derivative can be converted into a pharmaceutically acceptable salt thereof in a conventional manner, for example, by treatment with an

appropriate base. The ester or salt of the compound can be converted into the parent compound, for example, by hydrolysis.

In summary, the present invention, includes the following features:

(a) [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleosides and [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleosides, as outlined above, and pharmaceutically acceptable derivatives and salts thereof;

(b) [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleosides and [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleosides, and pharmaceutically acceptable derivatives and salts thereof for use in medical therapy, for example for the treatment or prophylaxis of an HIV or HBV infection;

(c) use of [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleosides and [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleosides, and pharmaceutically acceptable derivatives and salts thereof in the manufacture of a medicament for treatment of an HIV or HBV infection;

(d) pharmaceutical formulations comprising [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'didehydro-pyrimidine nucleosides and [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleosides or a pharmaceutically acceptable derivative or salt thereof together with a pharmaceutically acceptable carrier or diluent; and

(e) processes for the preparation of [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleosides and (5-carboxamido or 5-fluoro]-3'-

modified-pyrimidine nucleosides, as described in more detail below.

I. Active Compound, and Physiologically Acceptable Derivatives and Salts Thereof

The antivirally active compounds disclosed herein are [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydropyrimidine nucleosides and [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleosides, in the racemic or ß-D or ß-L enantiomerically enriched form.

The active compound can be administered as any derivative that upon administration to the recipient, is capable of providing directly or indirectly, the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as "physiologically acceptable salts"), and the 5' and N^4 acylated or alkylated derivatives of the active compound (alternatively referred to as "physiologically active derivatives"). In one embodiment, the acyl group is a carboxylic acid ester in which the non-carbonyl moiety of the ester group is selected from straight, branched, or cyclic alkyl, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with halogen, C_1 to C_4 alkyl or C_1 to C_4 alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethyl-t-butylsilyl) or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group. The term alkyl, as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon of C_1 to C_{18}, and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl.

Modifications of the active compound, specifically at the N^4 and 5'-O positions, can affect the bioavailability and rate of metabolism of the active species, thus providing control over the delivery of the active species. Further, the modifications can affect the antiviral activity of the compound, in some cases increasing the activity over the parent compound. This can easily be assessed by preparing the derivative and testing its antiviral activity according to the methods described herein, or other method known to those skilled in the art.

Since the 1' and 4' carbons of the carbohydrate of the nucleoside (referred to below generically as the sugar moiety) of the nucleosides are chiral, their nonhydrogen substituents (the pyrimidine or purine base and the CHOR groups, respectively) can be either cis (on the same side) or trans (on opposite sides) with respect to the sugar ring system. The four optical isomers therefore are represented by the following configurations (when orienting the sugar moiety in a horizontal plane such that the Y substituent is in the back): cis (with both groups "up", which corresponds to the configuration of naturally occurring nucleosides), cis (with both groups "down", which is a nonnaturally occurring configuration), trans (with the C2' substituent "up" and the C4' substituent "down"), and trans (with the C2, substituent "down" and the C4' substituent up"). The "D-nucleosides" are cis nucleosides in a natural configuration and the "L-nucleosides" are cis nucleosides in the nonnaturally occurring configuration.

II. Preparation of the Active Compounds

The nucleosides disclosed herein for the treatment of HIV and HBV infections in a host organism can be prepared according to published methods. ß-L-Nucleosides can be prepared from methods disclosed in, or standard modifications of methods disclosed in, for example, the following publications: Jeong, et al., J. of Med. Chem., 36, 182-195, 1993; European Patent Application Publication No. 0 285 884; Génu-Dellac, C., G. Gosselin,

A.-M. Aubertin, G. Obert, A. Kirn, and J.-L. Imbach, 3-Substituted thymine α-L-nucleoside derivatives as potential antiviral agents; synthesis and biological evaluation, Antiviral Chem. Chemother. 2:83-92 (1991); Johansson, K. N. G., B. G. Lindborg, and R. Noreen, European Patent Application 352 248; Mansuri, M. M., V. Farina, J. E. Starrett, D. A. Benigni, V. Brankovan, and J. C. Martin, Preparation of the geometric isomers of DDC, DDA, D4C and D4T as potential anti-HIV agents, Bioorg. Med. Chem. Lett. 1:65-68 (1991); Fujimori, S., N. Iwanami, Y. Hashimoto, and K. Shudo, A convenient and stereoselective synthesis of 2'-deoxy-ß-L-ribonucleosides, Nucleosides & Nucleotides 11:341-349 (1992); Génu-Dellac, C., G. Gosselin, A.-M. Aubertin, G. Obert, A. Kirn, and J.-L. Imbach, 3-Substituted thymine a-L-nucleoside derivatives as potential antiviral agents; synthesis and biological evaluation, Antiviral Chem. Chemother. 2:83-92 (1991); Holy, A, Synthesis of 2'-deoxy-L-uridine, Tetrahedron Lett. 2:189-192 (1992); Holy, A., Nucleic acid components and their analogs. CLIII. Preparation of 2'-deoxy-L-ribonucleosides of the pyrimidine series. Collect Czech Chem Commun. 37:4072-4087 (1992); Holy, A. 2'-deoxy-L-uridine: Total synthesis of a uracil 2'deoxynucleoside from a sugar 2-aminooxazoline through a 2,2'-anhydronucleoside intermediate. In: Townsend LB, Tipson RS, ed. Nucleic Acid Chem. New York: Wiley, 1992: 347-353. vol 1) (1992); Okabe, M., R.-C. Sun, S. Tan, L. Todaro, and D. L. Coffen, Synthesis of the dideoxynucleosides ddC and CNT from glutamic acid, ribonolactone, and pyrimidine bases. J. Org Chem. 53:4780-4786 (1988); Robins, M. J., T. A. Khwja, and R. K. Robins. Purine nucleosides. XXIX. Synthesis of 21-deoxy-L-adenosine and 21-deoxy-L-guanosine and their alpha anomers. J Org Chem. 35:363-639 (1992); Génu-Dellac, C., Gosselin G., Aubertin A-M, Obert G., Kirn A., and Imbach J-L, 3'-Substituted thymine a-L-nucleoside derivatives as potential antiviral agents; synthesis and biological evaluation. Antiviral Chem. Chemother. 2(2):83-92 (1991); Génu-Dellac, C., Gosselin G., Imbach J-L; Synthesis of new 2'-deoxy-3'-substituted-α-L-threopentofuranonucleosides of thymine as

a potential antiviral agents. Tet Lett 32(1):79-82 (1991); Génu-Dellac, C., Gosselin G., Imbach J-L, Preparation of new acylated derivatives of Larabino-furanose and 2-deoxy-l-erythro-pentofuranose as precursors for the synthesis of 1-pentofuranosyl nucleosides. 216:240-255 (1991); and Génu-Dellac, C., Gosselin G., Puech F, et al. Systematic synthesis and antiviral evaluation of α-L-arabinofuranosyl and 2'-deoxy-α-L-erythro-pento-furanosyl nucleosides of the five naturally occurring nucleic acid bases. 10(b):1345-1376 (1991).

ß-D-Dioxolane-nucleosides can be prepared as disclosed in detail in PCT/US91/09124. The process involves the initial preparation of (2R,4R)- and (2R,4S)-4-acetoxy-2-(protectedoxymethyl)-dioxolane from 1,6-anhydromannose, a sugar that contains all of the necessary stereochemistry for the enantiomerically pure final product, including the correct diastereomeric configuration about the 1 position of the sugar (that becomes the 4'-position in the later formed nucleoside). The (2R,4R)- and (2R,4S)-4-acetoxy-2-(protected-oxymethyl)dioxolane is condensed with a desired heterocyclic base in the presence of $SnCl_4$, other Lewis acid, or trimethylsilyl triflate in an organic solvent such as dichloroethane, acetonitrile, or methylene chloride, to provide the stereochemically pure dioxolane-nucleoside.

Enzymatic methods for the separation of D and L enantiomers of cis-nucleosides are disclosed in, for example, Nucleosides and Nucleotides, 12(2), 225-236 (1993); and PCT Publication Nos. WO 91/11186, WO 92/14729, and WO 92/14743 filed by Emory University.

Separation of the acylated or alkylated racemic mixture of D and L enantiomers of cis-nucleosides can be accomplished by high pressure liquid chromatography with selected chiral stationary phases, as disclosed, for example, in PCT Publication No. WO 92/14729.

Mono, di, and triphosphate derivatives of the active nucleosides can be prepared as described according to published methods. The monophosphate can be prepared according to the procedure of Imai et al., J.

Org. Chem., 34(6), 1547-1550 (June 1969). The diphosphate can be prepared according to the procedure of Davisson et al., J. Org. Chem., 52(9), 1794-1801 (1987). The triphosphate can be prepared according to the procedure of Hoard et al., J. Am. Chem. Soc., 87(8), 1785-1788 (1965).

Other references disclosing useful methods that can be used or adapted for the preparation of the active compounds include Hutchinson, D.W. "New Approaches to the Synthesis of Antiviral Nucleosides" TIBTECH 1990, 8, 348; Agrofoglio, L. et al. "Synthesis of Carbocyclic Nucleosides" Tetrahedron 1994, 50, 10611; Dueholm, K.L.; Pederson, E.B. Synthesis, 1994, 1; Wilson, L.J., Choi, W.-B., Spurling, T., Schinazi, R.F., Cannon, D., Painter, G.R., St.Clair, M., and Furman, P.A. The Synthesis and Anti-HIV Activity of Pyrimidine Dioxanyl Nucleoside Analogues. Bio. Med. Chem. Lett., 1993, 3, 169-174; Hoong, L.K., Strange, L.E., Liotta, D.C., Koszalka, G.W., Burns, C.L., Schinazi, R.F. Enzyme-mediated enantioselective preparation of the antiviral agent 2',3'-dideoxy-5-fluoro-3'-thiacytidine [(-)-FTC] and related compounds. J. Org. Chem., 1992, 57, 5563-5565; Choi, W.-B., Wilson, L.J., Yeola, S., Liotta, D.C., Schinazi, F.R. *In situ* complexation directs the stereochemistry of N-glycosylation in the synthesis of oxathiolanyl and dioxolanyl nucleoside analogues. J. Amer. Chem. Soc., **1991**, 113, 9377-9379; Choi, W.-B., Yeola, S., Liotta, D.C., Schinazi, R.F., Painter, G.R., Davis, M., St.Clair, M., Furman, P.A. The Synthesis, Anti-HIV and Anti-HBV Activity of Pyrimidine Oxathiolane Nucleoside Analogues. Bio. Med. Chem. Lett., **1993**, 3, 693-696; Wilson, J.E., Martin, J.L., Borrota-Esoda, K., Hopkins, S.E., Painter, G.R., Liotta, D.C., Furman, P.A. The 5'-Triphosphates of the and (+)-Enantiomers of Cis-5-Fluoro-1-(2-(hydroxymethyl)-1,3'-Oxathioan-5-yl] Cytosine Equally Inhibit Human Immunodeficiency Virus Type-1 Reverse Transcriptase. Antimicrob. Agents Chemother., **1993**, 37, 1720-1722.

The following working example provides a method for the preparation of 5-carboxamide-2',3'-dideoxy-3'-thiauridine. Melting points were determined on an Electrothermal IA 8100 digital melting point

apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a General Electric QE-300 (300 MHz) spectrometer; chemical shifts are reported in parts per million (d) and signals are quoted as s (singlet), d (doublet), t (triplet), or m (multiplet). UV spectrum were recorded on Shimadzu UV-2101PC spectrophotometer and FTIR spectra were measured on a Nicolet Impact 400 spectrometer. Mass spectroscopy was performed with JEOL (JMS-SX102/SX102A/E) spectrometer. Experiments were monitored using TLC analysis performed on Kodak chromatogram sheets precoated with silica gel and a fluorescent indicator. Column chromatography, employing silica gel (60-200 mesh; Fisher Scientific, Fair Lawn, NJ) was used for the purification of products. Tetrakis-(triphenylphosphine)palladium (0) and other chemicals were purchased from Aldrich Chemical Company (Milwaukee, WI). Microanalyses were performed at Atlantic Microlab Inc. (Norcross, GA). Enzymes were purchased from Amano International Enzyme Co. (Troy, VA).

Example 1 Preparation of 5-carboxamido-2',3'-dideoxy-3'-thiauridine

Coupling of 1-0-acetyl-5'-butyryl-3-thiafuranose with 5-iodo-cytidine using tin chloride afforded the protected β-isomer of 5'-butyryl-2',3'-deoxy-5-iodo-3'-thia-cytidine with good stereoselectivity.

To a solution of 5'-butyryl-2',3'-deoxy-5-iodo-3'-thiacytidine (1.63 g; 3.83 mmol) in 100 ml of anhydrous MeOH was added tetrakis-(triphenylphosphine) palladium (0) (0.16 g, 0.14 mmol) and Et_3N (0.8 ml). The reaction mixture was maintained under a CO atmosphere for 6 h while heating at 40 °C. The solution was concentrated to dryness *in vacuo,* dissolved in CH_2Cl_2 then filtered. The resultant precipitate was dissolved in hot $CHCl_3$ to give after crystallization the desired product 5-carboxylic acid methyl ester-2',3'-dideoxy-3'-thiacytidine (0.7 g, 62 %) as a white solid. m.p. 217-221 °C; ^1H NMR (DMSO) d 3.2-3.3 (m, 2H, H-2' and H-2''), 3.75 (s, 3H, OCH_3), 3.8-4. 0 (m, 2H, H-5' and H-5''), 5.36 (m, 1 H, OH-5'), 5.49 (t, 1

H, H-4', $J_{4',5'}$=4.0, 6.21 (m, 1H, H-1'), 7.7 and 8.1 (2 br s, 1H each, NH_2), 9.0 (s, 1H, H-6); *m/z* (LSIMS) 288 (M+H)+; Anal. ($C_{10}H_{13}N_3O_5S$) C, H, N, S.

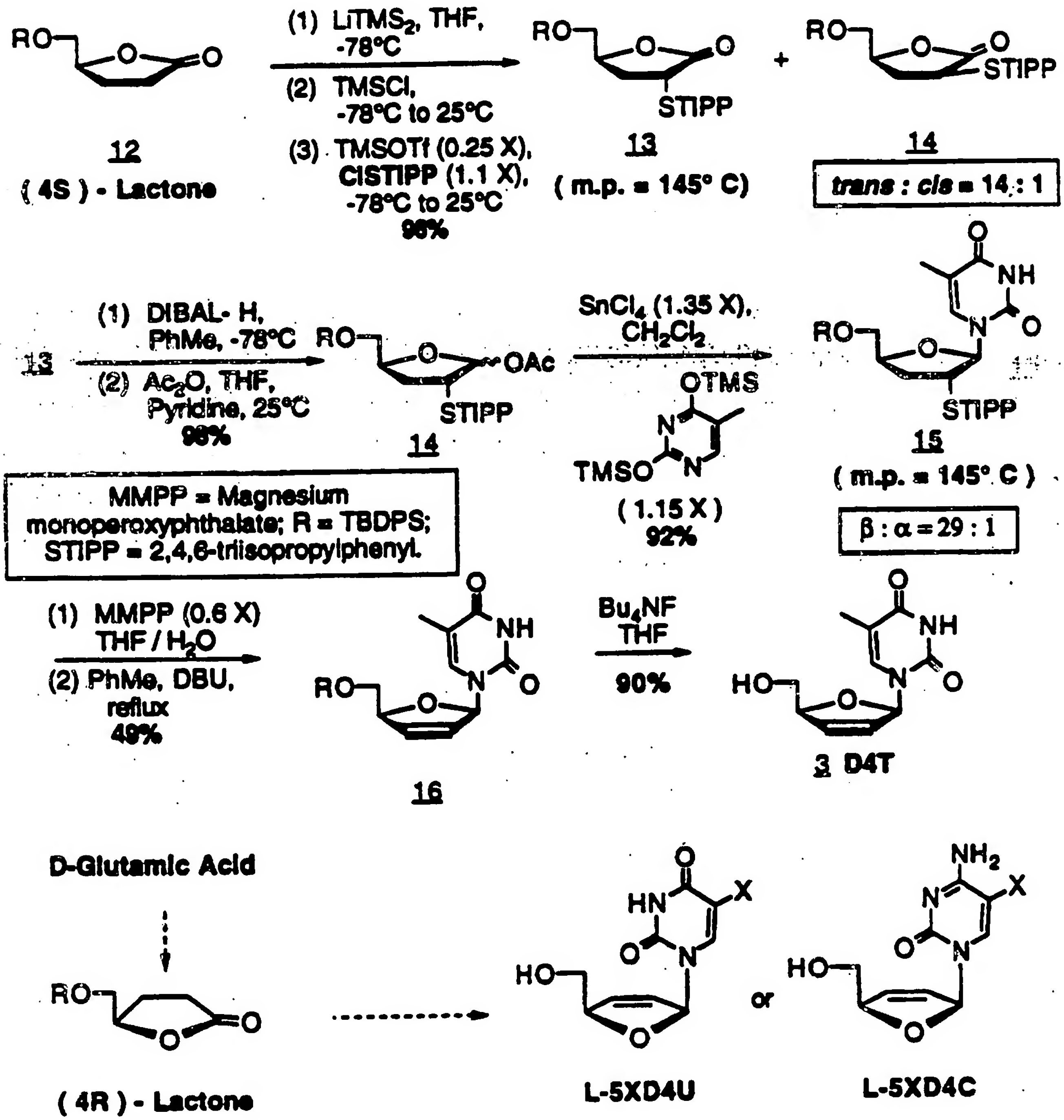
To a solution of 5-carboxylic acid methyl ester-2',3'-dideoxy-3'-thiacytidine (0.2 g, 0.69 mmol) in anhydrous MeOH was added (50 ml) a 2 M solution at of NH_3-MeOH and a catalytic amount of NaCN (20 mg). The resulting solution was stirred at 100 degrees for 20 h and then concentrated *in vacuo*. The residue was chromatographed on silica gel using CH_2Cl_2/MeOH (90:10) as eluent to give 5-carboxylic acid amide-2',3'-dideoxy-3'-thiacytidine (0.12 g, 63 %) as a white solid. m.p. 190-192 degrees; ^{1}H NMR (DMSO) d 3.18 (dd, 1 H, H-2' or H-2", $J_{2',2''}$=10. 2, $J_{2'or2'',1'}$=1.4), 3.41 (dd, 1 H, H-2' or H-2", $J_{2',2''}$=10.1, $J_{2'or2'',1'}$=1.5), 3.8-4.0 (m, 2H , H-5' and H-5"), 5.36 (t, 1 H, H-4', $J_{4',5'}$=4.0), 5.5 (br s, 1 H, OH-5'), 6.21 (dd, 1H, H-1', $J_{1',2'or2''}$=4.3, $J_{1',2'or2''}$=1.9), 7.5 (br s, 2H, NH2), 7.8 and 8.4 (2 br s, 1H each, NH_2), 8.6 (s, 1H, H-6); *m/z* (LSIMS) 273 $(M+H)^+$; Anal. ($C_9H_{12}N_4O_4S$) C, H, N, S.

Example 2. Preparation of β-D and β-L enantiomers of 5-carboxylic acid amide-2',3'-dideoxy-3'-thiacytidine

5-Butyryl-2',3'-deoxy-5-iodo-3'-thiacytidine (3 g, 7 mmol) was dissolved in 900 ml of 4/1 pH 8 buffer/CH_3CN. The clear solution was stirred and treated with 1000 units of pig liver esterase (PLE-A, Amano). The progress of the reaction was monitored by HPLC. After 16 hours (50% conversion), the reaction mixture was extracted with 2 x 600 ml of $CHCl_3$ and 600 ml of EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to dryness, and then submitted to the same pathway described in Example 1. The aqueous layer was evaporated to dryness then protected on the 5'-position using butyryl chloride and submitted to the same reaction pathway.

Example 3 Preparation of 2',3'-didehydro-2',3'-dideoxy-Pyrimidine Nucleosides

Scheme 1 below provides a general process for the preparation of 2',3'-didehydro-2',3'-dideoxy-pyrimidine nucleosides. This procedure can be adapted for a wide variety of bases, and can be used to provide either the β-D or the β-L isomer, as desired.



IV. **Ability of [5-carboxamido or 5-fluoro-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleoside or [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleosides to Inhibit the Replication of HIV and HBV**

The ability of nucleosides to inhibit HIV can be measured by various experimental techniques. The technique used herein, and described in detail below, measures the inhibition of viral replication in phytohemagglutinin (PHA) stimulated human peripheral blood mononuclear (PBM) cells infected with HIV-1 (strain LAV). The amount of virus produced is determined by measuring the virus-coded reverse transcriptase enzyme.. The amount of enzyme produced is proportional to the amount of virus produced.

Example 4 Anti-HIV Activity of 5-Substituted Derivatives of 2',3'-Dideoxy-3'-thiacytidine

A series of 5-substituted derivatives of 2',3'-dideoxy-3'-thiacytidine and 2',3'-dideoxy-3'-thiauridine (see Table 1) were synthesized and tested for anti-HIV activity.

Three-day-old phytohemagglutinin-stimulated PBM cells 10^6 cells/ml) from hepatitis B and HIV-1 seronegative healthy donors were infected with HIV-1 (strain LAV) at a concentration of about 100 times the 50% tissue culture infectious dose (TICD 50) per ml and cultured in the presence and absence of various concentrations of antiviral compounds.

Approximately one hour after infection, the medium, with the compound to be tested (2 times the final concentration in medium) or without compound, was added to the flasks (5 ml; final volume 10 ml). AZT was used as a positive control.

The cells were exposed to the virus (about 2 x 10^5 dpm/ml, as determined by reverse transcriptase assay) and then placed in a CO_2 incubator. HIV-1 (strain LAV) was obtained from the Center for Disease Control, Atlanta, Georgia. The methods used for culturing the PBM cells,

harvesting the virus and determining the reverse transcriptase activity were Dthose described by McDougal et al. (J. Immun. Meth. 76, 171-183, 1985) and Spira et al. (J. Clin. Meth. 25, 97-99, 1987), except that fungizone was not included in the medium (see Schinazi, et al., Antimicrob. Agents Chemother. 32, 1784-1787 (1988); Id., 34:1061-1067 (1990)).

On day 6, the cells and supernatant were transferred to a 15 ml tube and centrifuged at about 900 g for 10 minutes. Five ml of supernatant were removed and the virus was concentrated by centrifugation at 40,000 rpm for 30 minutes (Beckman 70.1 Ti rotor). The solubilized virus pellet was processed for determination of the levels of reverse transcriptase. Results are expressed in dpm/ml of sampled supernatant. Virus from smaller volumes of supernatant (1 ml) can also be concentrated by centrifugation prior to solubilization and determination of reverse transcriptase levels.

The median effective (EC_{50}) concentration was determined by the median effect-method (Antimicrob. Agents Chemother. 30, 491-498 (1986). Briefly, the percent inhibition of virus, as determined from measurements of reverse transcriptase, is plotted versus the micromolar concentration of compound. The EC_{50} is the concentration of compound at which there is a 50% inhibition of viral growth.

Mitogen stimulated uninfected human PBM cells (3.8×10^5 cells/ml) were cultured in the presence and absence of drug under similar conditions as those used for the antiviral assay described above. The cells were counted after 6 days using a hemacytometer and the trypan blue exclusion method, as described by Schinazi et al., Antimicrobial Agents and Chemotherapy, 22(3), 499 (1982). The IC_{50} is the concentration of compound which inhibits 50% of normal cell growth.

Table I provides the EC_{50} values (concentration of nucleoside that inhibits the replication of the virus by 50% in PBM cells, estimated 10% error factor) and IC_{50} values (concentration of nucleoside that inhibits 50% of the growth of mitogen-stimulated uninfected human PBM cells, CEM cells, and in Vero cells) of a number of the tested 5-substituted-3'-thia-2',3'-

dideoxypyrimidine nucleosides. In contrast, in the cytosine series, the racemic 5-acetamide derivative was shown to have antiviral activity with a median effective concentration of 0.77 micromolar and no toxicity up to 100 micromolar in various cell lines. Similar results were obtained on evaluation of the anti-HBV activity. The racemic compound was resolved by an enzyme mediated approach into the β-D and β-L enantiomers, as described in Example 2. Both 5-acetamide derivatives were effective inhibitors of HIV-1 and HBV replication.

Table 1. Biological Evaluation of Various 5-Substituted-3'-thia-2',3'-dideoxypyrimidine Nucleosides Against HIV-1_{LAI}, HSV-1_F, and for Cytotoxicity in PBM, CEM, and Vero Cells.

Base	5-Substitutent	Configuration	Anti-HIV-1 in PBMC EC_{50}, μM	Toxicity in PBM cells IC_{50}, μM	Toxicity in CEM cells IC_{50}, μM	Toxicity in Vero cells IC_{50}, μM	Anti-HSV-1 in Vero cells EC_{50}, μM^a
U	Nitro	(±)-ß-DL	122.2	> 100	> 100	> 100	
C	Nitro	(±)-ß-DL	100.0	> 100	> 100	> 100	
U	Amino	(±)-ß-DL	118.6	> 100	> 100	> 100	
C	Amino	(±)-ß-DL	26.4	> 100	> 100	> 100	
U	Ethynyl	(±)-ß-DL	23.8	> 100	> 100	> 100	
C	Ethynyl	(±)-ß-DL	> 100	> 100	> 100	> 100	
U	Ethyl	(±)-ß-DL	> 100	> 100	> 100	> 100	
C	Ethyl	(±)-ß-DL	102.5	> 100	> 100	> 100	
U	Cyano	(±)-ß-DL	> 100	> 100	> 100	> 100	
C	Cyano	(±)-ß-DL	> 100	> 100	> 100	> 100	
C	Methoxycarbonyl	(±)-ß-DL	> 100	> 100	> 100	> 100	> 100

Base	5-Substitutent	Configuration	Anti-HIV-1 in PBMC EC_{50}, μM	Toxicity in PBM cells IC_{50}, μM	Toxicity in CEM cells IC_{50}, μM	Toxicity in Vero cells IC_{50}, μM	Anti-HSV-1 in Vero cells EC_{50}, μM[a]
C	Methoxycarbonyl	(±)-ß-DL	38.9	>100	>100	>100	
C	Carboxamide	(±)-ß-DL	>100	>100	>100	>100	
C	Carboxamide	(±)-ß-DL	0.77	>100	>100	>100	>100
C	Carboxamide	(+)-ß-DL	8.5	>100	>100	>100	
C	Carboxamide[b]	(-)-ß-DL	3.6	>100	>100	>100	
C	N-Methylaminoformyl	(±)-ß-DL	>100	>100	>100	>100	
C	N,N-Methylaminoformyl	(±)-ß-DL	>100	>100	>100	>100	
C	H (3TC)	(-)-ß-DL	0.002	>100	>100	>100	>100

[a] Acyclovir used as apostivie control had an EC_{50} of 0.04 μM.

[b] EC_{50} against HIV-2_{ROD2} and SIV_{SMM} was 1.6 and 4.0 μM,respectively.

Example 5 Anti-HBV Activity of 5-Substituted Derivatives of 2',3'-Dideoxy-3'-thiacytidine

The ability of the active compounds to inhibit the growth of virus in 2.2.15 cell cultures (HepG2 cells transformed with hepatitis virion) can be evaluated as described in detail below.

A summary and description of the assay for antiviral effects in this culture system and the analysis of HBV DNA has been described (Korba and Milman, 1991, Antiviral Res., 15:217). The antiviral evaluations were performed on two separate passages of cells. All wells, in all plates, were seeded at the same density and at the same time.

Due to the inherent variations in the levels of both intracellular and extracellular HBV DNA, only depressions greater than 3.5-fold (for HBV virion DNA) or 3.0-fold (for HBV DNA replication intermediates) from the average levels for these HBV DNA forms in untreated cells are considered to be statistically significant (P<0.05]. The levels of integrated HBV DNA in each cellular DNA preparation (which remain constant on a per cell basis in these experiments) were used to calculate the levels of intracellular HBV DNA forms, thereby ensuring that equal amounts of cellular DNA were compared between separate samples.

Typical values for extracellular HBV virion DNA in untreated cells ranged from 50 to 150 pg/ml culture medium (average of approximately 76 pg/ml). Intracellular HBV DNA replication intermediates in untreated cells ranged from 50 to 100 μg/pg cell DNA (average approximately 74 pg/μg cell DNA). In general, depressions in the levels of intracellular HBV DNA due to treatment with antiviral compounds are less pronounced, and occur more slowly, than depressions in the levels of HBV virion DNA (Korba and milman, 1991, Antiviral Res., 15:217).

The manner in which the hybridization analyses were performed for these experiments resulted in an equivalence of approximately 1.0 pg of intracellular HBV DNA to 2-3 genomic copies per cell and 1.0 pg/ml of extracellular HBV DNA to 3 x 10^5 viral particles/ml.

Toxicity analyses were performed to assess whether any observed antiviral effects were due to a general effect on cell viability. The method used herein was the measurement of the uptake of neutral red dye, a standard and widely used assay for cell viability in a variety of virus-host systems, including HSV and HIV. Toxicity analyses were performed in 96-well flat bottomed tissue culture plates. Cells for the toxicity analyses were cultured and treated with test compounds with the same schedule as described for the antiviral evaluations below. Each compound was tested at 4 concentrations, each in triplicate cultures (wells "A", "B", and "C"). Uptake of neutral red dye was used to determine the relative level of toxicity. The absorbance of internalized dye at 510 nm (A_{sin}) was used for the quantitative analysis. Values are presented as a percentage of the average A_{sin} values in 9 separate cultures of untreated cells maintained on the same 96-well plate as the test compounds. Dye uptake in the 9 control cultures on plate 5 ranged from 91.6% to 110.4%, and on plate 6 from 96.6% to 109%.

The results of the HBV assay are provided in Table 2. As indicated, the ß-D and ß-L enantiomers of 5-carboxylic acid amide-2',3'-dideoxy-3'-thiacytidine (referred to as ß-L- and ß-D-carboxamide) exhibit significant activity against HBV and are relatively nontoxic.

TABLE 2. EFFECT OF CARBOXAMIDE DERIVATIVES OF 3TC AGAINST HEPATITIS B VIRUS IN TRANSFECTED HEPG-2 (2.2.15) CELLS ON DAY 9

Compound	HBV virton[a]		HBV RI[b]		Cytotoxicity	Selectivity Index IC_{50}/EC^{90}	
	$EC_{50}\pm SD^c$	$EC_{90}\pm SD^c$	$EC_{50}\pm SD^c$	$EC_{90}\pm SD^c$	$IC_{50}\pm SD^c$	Virion	RI
ß-D-DDC	1.4±0.2	9.6±1.1	3.4±0.4	13.0±1.4	236±21	26	18
ß-L-carboxamide	0.29±0.02	1.5±0.2	1.3±0.1	9.9±0.8	1747±212	1165	177
ß-L-carboxamide	0.11±0.012	0.9±0.1	0.5±0.04	3.8±0.3	1124±72	1249	296
ß-L-FTC	0.04±0.006	1.1±0.1	0.16±0.01	0.39±0.22	746±33	678	1,913

[a] Extracellual DNA; untreated control had 102 pg/ml

[b] Replißative intermediates (Intracellular DNA), untreated control had 87 pg/μg cell DNA

[c] μM

Example 6 Anti-HIV Activity of 2',3'-Didehydro-2',3'-dideoxypyrimidine nucleosides

Table 3 provides the EC50 values (concentration of nucleoside that inhibits the replication of the HIV-1 and HIV-2 by 50% in PBM cells, estimated 10% error factor) and IC_{50} values (concentration of nucleoside that inhibits 50% of the growth of mitogen-stimulated uninfected human PBM cells, CEM cells, and in Vero cells) of B-L-2',3'-didehydro-2',3'-dideoxy-cytidine and ß-2',3,-didehydro-2',3'-dideoxy-5-fluoro-cytidine. As indicated, both compounds exhibit significant activity against HIV, and are relatively nontoxic.

Example 7 Anti-HBV Activity of 2',3'-Didehydro-2',3'-dideoxypyrimidine nucleosides

Table 4 provides the effect of DDC derivatives against Hepatitis B Virus (HBV) in transfected HEPG-2(2.2.15) cells on day 9.

Table 3. **Biological Evaluation of Various ß-L-2',3'-dideoxypyrimidine nucleosides Against HIV-1_{LAI}, HIV-2_{ROD2}, SIV_{SMM}, and for Cytotoxicity in PBM, CEM, and Vero Cells.**

Compound	Configuration	Anti-HIV-1 in PBMC EC_{50}, µM	Anti-HIV-2 in PBMC EC_{50}, µM	Anti-SIV in PBMC EC_{50}, µM	Toxicity in PBM cells IC_{50}, µM	Toxicity in CEM cells IC_{50}, µM	Toxicity in Vero cells IC_{50}, µM
L-D4C	(-)-ß-L	0.0058	0.033	0.048	>100	0.73	10.8
L-F-D4C	(-)-ß-L	0.0015	0.0006	0.00015	>100	7.3	40.3
3TC	(-)-ß-L	0.002	0.020	0.02	>100	>100	>100

Table 4 EFFECT OF DDC DERIVATIVES AGAINST HEPATITIS B VIRUS (HBV) IN TRANSFECTED HEPG-2 (2.2.15) CELLS ON DAY 9

	HBV virton[a]		HBV R1[b]		Cytotoxicity	Selectivity Index $1C_{50}/EC^{90}$	
Compound	$EC_{50}\pm SD$[c]	$EC_{90}\pm SD$[c]	$EC_{50}\pm SD$[c]	$EC_{90}\pm SD$[c]	$1C_{50}\pm SD$[c]	Virion	R1
ß-D-DDC	1.5±0.2	8.2±0.8	2.4±0.3	12.0±1.1	259±18	37	22
ß-L-D4C	0.15±0.02	0.33±0.04	0.91±0.09	2.3±0.3	1044±92	1149	454
ß-L-F-D4C	0.28±0.03	0.41±0.04	0.33±0.04	0.75±0.07	>7.3	>7.3	>4

[a] Extracellual DNA; untreated control had 102 pg/ml

[b] Replicative intermediates (Intracellular DNA), untreated control had 87 pg/µg cell DNA

[c] µM

III. Preparation of Pharmaceutical Compositions.

Humans suffering from diseases caused by HIV or HBV infection can be treated by administering to the patient an effective amount of a (5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleoside or (5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleoside or a pharmaceutically acceptable derivative or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount of compound to inhibit viral replication *in vivo*, especially HIV and HBV replication, without causing serious toxic effects in the patient treated. By "inhibitory amount" is meant an amount of active ingredient sufficient to exert an inhibitory effect as measured by, for example, an assay such as the ones described herein.

A preferred dose of the compound for all of the abovementioned conditions will be in the range from about I to 50 mg/kg, preferably 1 to 20 mg/kg, of body weight per day, more generally 0.1 to about 100 mg per kilogram body weight of the recipient per day. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent nucleoside to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

The compound is conveniently administered in unit any suitable dosage form, including but not limited to one containing 7 to 3000 mg, preferably 70 to 1400 mg of active ingredient per unit dosage form. A oral dosage of 50-1000 mg is usually convenient.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.2 to 70 pM, preferably about 1.0 to 10 μM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

A preferred mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as

sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable derivative or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, antiinfl-ammatories, or other antivirals, including other nucleoside anti-HIV compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate,

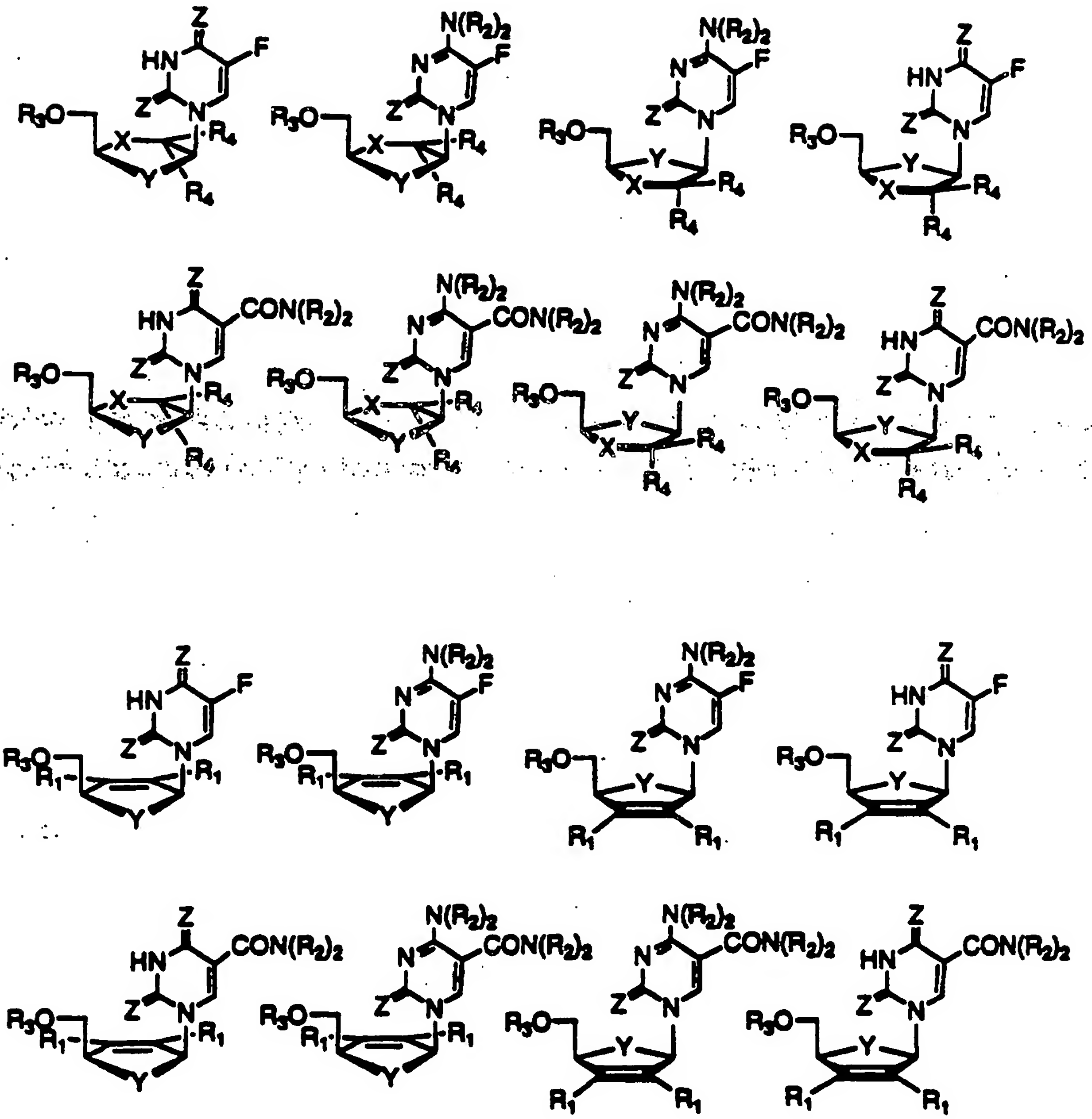
polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation.

Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

This invention has been described with reference to its preferred embodiments. variations and modifications of the invention, will be obvious to those skilled in the art from the foregoing detailed description of the invention. It is intended that all of these variations and modifications be included within the scope of the appended claims.

We claim.

1. A compound of the structure:



wherein: X is 0, S, CH2, CHF, or CF2;

Y is 0, S, CH2, CHF, CF2;

Z is independently 0, S or Se;

R_1 is independently H or F;

R_2 is independently H, OH, Cl to C6 alkyl, or C(O) (C_1 to C_6 alkyl);

R_3 is H, C(O)(C_1-C_6 alkyl); alkyl, or mono-, di- or triphosphate; and

R_4 is independently H, F, Cl, Br, I, OH, -O(C_1,-C_6alkyl), -SH, -S(C_1-C_6alkyl); or -C,-C_6alkyl; and when Y is O, X is O or S; and R^4 is H, the 5-substituent is not fluorine.

2. The compound of claim 1, wherein Y is 0 or S; Z is 0; RI is H; R_2 is H; and R_3 is H.

3. The compound of claim 1, wherein X is 0 or S; Y is 0; Z is 0; R_1 is H; R_2 is H; R_3 is H, and R_4 is independently H or F.

4. The compound of claim 1 in the form of a racemic mixture.

5. The compound of claim 1 in the form of a B-D-enantiomer.

6. The compound of claim 1 in the form of a B-L-enantiomer.

7. The compound of claim 1 in enantiomerically enriched form.

8. The compound of claim 1 selected from the group consisting of the racemic mixture, B-D- or B-L-enantiomer of 2-hydroxymethyl-5-(N-5-carboxamidouracil-1-yl)-1,3-oxathiolane; 2-hydroxymethy1-4-(N-5-carboxamidouracil-1-yl)-1,3-dioxolane; 2-hydroxymethyl-4-(N-5-fluorocytosin-1-yl)-1,3-dithiolane; 2-hydroxymethyl-4-(N-5,1-carboxamidouracil-1-yl)-1,3-dithiolane; 2-hydroxymethyl-4-(N-5-fluorocytosin-1-yl)-1,3-oxathiolane; 2-hydroxymethyl-4-(N-5-carboxamidouracil-1-yl)-1,3-oxathiolane; 2',3'-dideoxy-2',3'-didehydro-5-fluorocytidine; 2',3'-dideoxy-2',3'-didehydro-5-carboxamidocytidine; 2',3'-dideoxy-5-fluorocytidine; 2',3'-dideoxy-5-carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro-2',5-difluorocytidine; 2',3'-dideoxy-2',3'-didehydro-2'-fluoro-5-carboxamidocytidine, 2',3'-dideoxy-2',3'-didehydro-3',5-difluorocytidine; 2',3'-dideoxy-2',3'-didehydro-3'-fluoro-5-

carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro-2',3',5-trifluorocytidine; 2',3'-dideoxy-2',3'-didehydro-2',3'-difluoro-5-carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro-5-fluorocytidine; 2',3'-dideoxy-2',3'-didehydro-5-carboxamidocytidine; 2',3'-dideoxy-5-fluorocytidine; 2',3'-dideoxy-5-carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro-2',5-difluorocytidine; 2',3'-dideoxy-2',3'-didehydro-2'-fluoro-5-carboxamidocytidine; 2',3'-dideoxy-2',3'-didehydro- 3',5-difluorouridine; 2',3'-dideoxy-2',3'-didehydro-3'-fluoro-5-carboxamidouridine; 2',3'-dideoxy-2',3'-didehydro-2',3',5trifluorouridine; and 2',3'-dideoxy-2',3'-didehydro-2',3'-difluoro-5-carboxamidouridine.

9. The compound of claim 1 selected from the group consisting of the racemic mixture, the B-L-enantiomer and the BD-enantiomer of 5-carboxylic acid amide-2',3'-dideoxy-3'-thiacytidine.

10. A composition comprising an effective HIV or HBV treatment amount of a compound of claim 1 in combination with a compound selected from the group consisting of 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC); the (-)-enantiomer of 2-hydroxymethyl-5-(cytosin-1-yl)1,3-oxathiolane (3TC); carbovir, acyclovir, interferon, AZT, DDI, DDC, L-(-)-FMAU, and D4T.

11. A pharmaceutical composition comprising an effective amount to treat HIV or HBV infection in humans of a compound of claim 1 in the racemic or enantiomerically enriched form, or its physiologically acceptable salt, in a pharmaceutically acceptable carrier.

12. A method for treating HIV infection in humans comprising administering an effective amount of a compound of claim 1 or its physiologically acceptable derivative or physiologically acceptable salt, in a pharmaceutically acceptable carrier.

13. A method for treating HBV infection in humans comprising administering an effective amount of a compound of claim 1 or its physiologically acceptable derivative or physiologically acceptable salt, in a pharmaceutically acceptable carrier.

14. The use of a [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleoside or [5-carboxamido or 5-fluoro]-3'-

modified-pyrimidine nucleoside of claim 1, and pharmaceutically acceptable derivatives and salts thereof in the manufacture of a medicament for treatment of an HIV or HBV infection.

15. A pharmaceutical formulation comprising a [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'didehydro-pyrimidine nucleoside or [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleoside of claim 1 or a pharmaceutically acceptable derivative or salt thereof together with a pharmaceutically acceptable carrier or diluent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00965

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/49, 50, 51, 274, 371, 262, 265, 266; 536/26.23, 26.26, 26.8, 28.51, 28.52, 28.53, 28.54, 28.55; 544/313, 314, 317.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

File CA electronic structure search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,210,085 (LIOTTA et al.) 11 May 1993, see entire document, particularly claims 1-21.	1-15
X	US, A, 5,234,913 (FURMAN et al.) 10 August 1993, see entire document, particularly claim 1-5.	10
A	US, A, 5,270,315 (BELLEAU et al.) 14 December 1993, see entire document.	1-15
X	US, A, 5,041,449 (BELLEAU et al.) 20 August 1991, see entire document, particularly claims 1-6.	1-15
X	WO, A, 92/18517 (YALE UNIVERSITY) 29 October 1992, see entire document.	1-11 and 13-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search	Date of mailing of the international search report
24 MAY 1996	03 JUN 1996

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 94/09793 (EMORY UNIVERSITY) 11 May 1994, see entire document, particularly page 5.	10
X	WO, A, 92/14743 (EMORY UNIVERSITY) 03 September 1992, see entire document, particularly claims 1-34.	1-15
X	EP, A, 0,409,227 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 23 January 1991, see entire document, particularly claims 1,2 and 5.	1, 3-8, 11 and 14-15
X	NL, A, 8,901,258 (STICHTING REGA V.Z.W.) 17 December 1990, see entire document, particularly claims 1-14.	1-15
A	WO, A, 94/14831 (UNIVERSITY OF ALBERTA) 07 July 1994, see entire document.	1-15
X	WO, A, 92/14729 (EMORY UNIVERSITY) 03 September 1992, see entire document, particularly claims 24-28.	1-9 and 11-15
X	WO, A, 92/15308 (WELLCOME FOUNDATION) 17 SEPT 1992, see entire document, particularly claims 1-10.	1-9, 11 and 13-15
X, P	WO, A, 95/07086 (EMORY UNIVERSITY) 16 March 1995, see entire document, particularly claims 1-12.	1-11 and 13-15.
X	WO, A, 93/23201 (WELLCOME FOUNDATION LTD) 25 November 1993, see entire document, particularly claims 1-3 and 5-15.	1-12 and 14-15.
X	EP, A, 0,526,253 (BIOCHEM PHARMA INC.) 02 March 1993, see entire document, particularly claims 1-11 at page 12.	1-9, 11-15.
X, P	JP, A, 95-10921 (WELLCOME FOUNDATION LTD) 25 April 1995, see abstract.	1-9, 11-12 and 14-15.
X	WILSON et al. The Synthesis and Anti-HIV Activity of Pyrimidine Dioxolanyl Nucleosides. Bioorg. Medicinal Chem Let. 1993, Vol. 3, No. 2, pages 169-174, see entire document.	1-9, 11-12 and 14-15.
X	CHOI et al. Synthesis, Anti-Human Immunodeficiency Virus, and Anti-Hepatitis B Virus Activity of Pyrimidine Oxathiolane Nucleosides. Bioorg. Medicinal Chem. Let. 1993, Vol. 3, No. 4, pages 693-696, see entire document.	1-15
X	FEORINO et al. Prevention of Activation of HIV-1 by Antiviral Agents in OM-10.1 Cells. 1993, Vol. 4, No. 1, pages 55-63, see entire document.	1-9, 11-12 and 14-15.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VAN ROEY et al. Absolute Configuration of the Antiviral Agent (-)-Cis-5-fluoro-1-[2-hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Antiviral Chem. Chemotherapy. 1993, Vol. 4, No. 6, pages 369-375, see entire document.	1-9 and 11-15.
X	TISDALE et al. Rapid In Vitro Selection of Human Immunodeficiency Virus Type 1 Resistant to 3'-Thiacytidine Inhibitors Due to a Mutation in the YMDD Region of Reverse Transcriptase. Proc. Natl. Acad. Sci. USA. June 1993, Vol. 90, pages 5653-5656, see entire document.	1-9, 11-12 and 14-15.
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X, P	MANSOUR et al. Structure-Activity Relationships Among a New Class of Antiviral Heterosubstituted 2', 3'-Dideoxynucleoside Analogues. Nucleosides & Nucleotides. 1995, Vol. 14, No. 3-5, pages 627-635, see entire document.	1-9 and 11-15.
X, P	MANSOUR et al. Anti-Human Immunodeficiency Virus and Anti-Hepatitis-B Virus Activities and Toxicities of the Enantiomers of 2'-Deoxy-3'-oxa-4'-thiocytidine and Their 5-Fluoro Analogues in Vitro. J. Medicinal Chem. 06 January 1995, Vol. 38, No. 1, pages 1-4, see entire document.	1-9 and 11-15.
X	FRICK et al. Pharmacokinetics, Oral Bioavailability, and Metabolism in Mice and Cynomolgus Monkeys of (2'R, 5'S-)-cis-5-Fluoro-1-[2-(Hydroxymethyl)-1, 3-Oxathiolan-5-yl] Cytosine, an Agent Active Against Human Immunodeficiency Virus and Human Hepatitis B Virus. Antimicrobial Agents Chemotherapy. December 1994, Vol. 38, No. 12, pages 2722-2729, see entire document.	1-9 and 11-15.
X	PAFF et al. Intracellular Metabolism of (-)- and (+)-cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Oxathiolan-5-yl] Cytosine in HepG2 Derivative 2.2.1.5 (Subclone P5A) Cells. Antimicrobial Agents Chemotherapy. June 1994, Vol. 38, No. 6, pages 1230-1238, see entire document.	1-9, 11 and 13-15.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	SCHINAZI et al. Characterization of Human Immunodeficiency Viruses Resistant of Oxathiolane-Cytosine Nucleosides. Antimicrobial Agents Chemotherapy. Vol. 37, No. 4, pages 875-881, see entire document.	1-9, 11-12 and 14-15.
X	FRICK et al. Pharmacokinetics, Oral Bioavailability, and Metabolic Disposition in Rats of (-)-cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Oxathiolan-5-yl] Cytosine, a Nucleoside Analog Active Against Human Immunodeficiency Virus and Hepatitis B Virus. Antimicrobial Agents Chemotherapy. November 1993, Vol. 37, No. 11, pages 2285-2292, see entire document.	1-9 and 11-15.
X	JANSEN et al. High-Capacity In Vitro Assessment of Anti-Hepatitis B Virus Compound Selectivity by a Viron-Specific Polymerase Chain Reaction Assay. Antimicrobial Agents Chemotherapy. March 993, Vol. 37, No. 3, pages 441-447, see entire document.	1-9, 11, and 13-15.
X	SHEWACH et al. Affinity of the Antiviral Enantiomers of Oxathiolane Cytosine Nucleosides for Human 2'-deoxycytidine Kinase. Biochemical Pharmacology. 1993, Vol. 45, No. 7, pages 1540-1543, see entire document.	1-9 and 11-15.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHINAZI et al. Selective Inhibition of Human Immunodeficiency Viruses by Racemates and Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Oxathiolan-5-yl) Cytosine. November 1992, Vol. 36, No. 11, pages 2423-2431, see entire document.	1-9, 11-12 and 14-15.
X	FURMAN et al. The Anti-Hepatitis B Virus Activities, Cytotoxicities, and Anabolic Profiles of the (-) and (+) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1, 3-Oxathiolan-5-yl] Cytosine. Antimicrobial Agents Chemotherapy. December 1992, Vol. 36, No. 12, pages 2686-2692, see entire document.	1-9, 11 and 13-15.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/70, 31/52, 31/505; C07H 19/073, 19/10; C07D 473/16, 473/34, 405/04, 473/00.

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/49, 50, 51 274, 371, 262, 265, 266; 536/26.23, 26.26, 26.8, 28.51, 28.52, 28.53, 28.54, 28.55; 544/313, 314, 317.